CHAPTER 5

Thyroid and parathyroid cancers

Rena Vassilopoulou-Sellin, MD, Robert Lustig, MD, and Jeffrey P. Lamont, MD

Endocrine malignancies, although relatively uncommon, are often difficult to diagnose and treat effectively. According to American Cancer Society (ACS) estimates, more than 27,000 new cases of endocrine neoplasms will be diagnosed in the United States in 2005, and approximately 2,370 deaths will result from these cancers. This chapter will focus on thyroid and parathyroid cancers. (A discussion of carcinoid tumors, insulinomas, gastrinomas, and other gastrointestinal neuroendocrine tumors, as well as adrenocortical cancer, can be found in chapter 14.)

THYROID CANCER

Thyroid cancer is the most common endocrine cancer. The number of deaths from thyroid cancer projected for the year 2005 is 1,460, or 7% of all new thyroid cancer cases.

The prevalence rate for occult thyroid cancers found at autopsy is 5%-10%, except in Japan and Hawaii, where the rate can be as high as 28%. Autopsy rates do not correlate with clinical incidence.

The incidence of thyroid nodules in the general population is 4%-7%, with nodules being more common in females than males. The prevalence of thyroid cancer in a solitary nodule or in multinodular thyroid glands is 10%-20%; this increases with irradiation of the neck in children and older men (see section on "Etiology and risk factors").

Tumor types

Thyroid cancer is classified into four main types according to its morphology and biological behavior: papillary, follicular, medullary, and anaplastic. Differentiated (papillary and follicular) thyroid cancers account for > 90% of thyroid malignancies and constitute approximately 0.8% of all human malignancies. Medullary thyroid cancers represent 5%-10% of all thyroid neoplasms. About 80% of patients with medullary cancer have a sporadic form of the disease, whereas the remaining 20% have inherited disease. Anaplastic carcinoma represents ≤ 5% of all thyroid carcinomas.

Papillary thyroid carcinoma is the most common subtype and has an excellent prognosis. Most papillary carcinomas contain varying amounts of follicular tissue. When the predominant histology is papillary, the tumor is considered to be a papillary carcinoma. Because the mixed papillary-follicular variant tends to behave like a pure papillary cancer, it is treated in the same manner and has a similar prognosis.

Papillary tumors arise from thyroid follicular cells, are unilateral in most cases, and are often multifocal within a single thyroid lobe. They vary in size from microscopic to large cancers that may invade the thyroid capsule and infiltrate into contiguous structures. Papillary tumors tend to invade the lymphatics, but vascular invasion (and hematogenous spread) is uncommon.

Up to 40% of adults with papillary thyroid cancer may present with regional lymph node metastases, usually ipsilateral. Distant metastases occur, in decreasing order of frequency, in the lungs, bones, and other soft tissues. Older patients have a higher risk for locally invasive tumors and for distant metastases. Children may present with a solitary thyroid nodule, but cervical node involvement is more common in this age group; up to 10% of children and adolescents may have lung involvement at the time of diagnosis.

Follicular thyroid carcinoma is less common than papillary thyroid cancer, occurs in older age groups, and has a slightly worse prognosis. Follicular thyroid cancer can metastasize to the lungs and bones, often retaining the ability to accumulate radioactive iodine (which can be used for therapy). Metastases may be appreciated many years after the initial diagnosis.

Follicular tumors, although frequently encapsulated, commonly exhibit microscopic vascular and capsular invasion. Microscopically, the nuclei tend to be large and have atypical mitotic figures. There is usually no lymph node involvement.

Follicular carcinoma can be difficult to distinguish from its benign counterpart, follicular adenoma. This distinction is based on the presence or absence of capsular or vascular invasion, which can be evaluated after surgical excision but not by fine-needle aspiration (FNA).

Thyroglobulin, normally synthesized in the follicular epithelium of the thyroid, is present in well-differentiated papillary and follicular carcinomas and infrequently in anaplastic carcinomas but not in medullary carcinomas. Therefore, thyroglobulin immunoreactivity is considered to be indicative of a follicular epithelial origin.

Hürthle cell carcinoma Hürthle cell, or oxyphil cell, carcinoma is a variant of follicular carcinoma. Hürthle cell carcinoma is composed of sheets of Hürthle cells and has the same criteria for malignancy as does follicular carcinoma. Hürthle cell carcinoma is thought to have a worse outcome than follicular carcinoma and is less apt to concentrate radioactive iodine.

Medullary thyroid carcinoma originates from the C cells (parafollicular cells) of the thyroid and secretes calcitonin. On gross examination, most tumors are firm, grayish, and gritty.

Sporadic medullary thyroid carcinoma usually presents as a solitary thyroid mass; metastases to cervical and mediastinal lymph nodes are found in half of patients and may be present at the time of initial presentation. Distant metastases to the lungs, liver, bones, and adrenal glands most commonly occur late in the course of the disease. Secretory diarrhea, related to calcitonin secretion, can be a clinical feature of advanced medullary thyroid carcinoma.

Familial medullary thyroid carcinoma presents as a bilateral, multifocal process. Histologically, familial medullary carcinoma of the thyroid does not differ from the sporadic form. However, the familial form is frequently multifocal, and it is common to find areas of C-cell hyperplasia in areas distant from the primary carcinoma. Another characteristic feature of familial medullary carcinoma is the presence of amyloid deposits.

Anaplastic carcinoma Anaplastic tumors are high-grade neoplasms characterized histologically by a high mitotic rate and lymphovascular invasion. Aggressive invasion of local structures is common, as are lymph node metastases. Distant metastases tend to occur in patients who do not succumb early to regional disease. Occasional cases of anaplastic carcinoma have been shown to arise from preexisting differentiated thyroid carcinoma or in a preexisting goiter.

Other tumor types Lymphomas of the thyroid account for < 5% of primary thyroid carcinomas. Other tumor types, such as teratomas, squamous cell carcinomas, and sarcomas, may also rarely cause primary thyroid cancers.

Genetic factors In addition to sporadic medullary thyroid cancer, which represents the majority of cases, there are three hereditary forms: familial medullary thyroid carcinoma; multiple endocrine neoplasia type 2A (MEN-2A), characterized by medullary thyroid cancer, pheochromocytomas, and hyperparathyroidism; and multiple endocrine neoplasia type 2B (MEN-2B), characterized by medullary thyroid cancer, marfanoid habitus, pheochromocytomas, and neuromas. These syndromes are associated with germ-line mutations of the *RET* proto-oncogene, which codes for a receptor tyrosine kinase (RTK). Familial medullary thyroid carcinoma is inherited as an autosomal-dominant trait with high penetrance and variable expression. (For a discussion of genetic testing to screen for *RET* mutations in MEN-2A kindreds, see section on "Staging and prognosis.")

Epidemiology

Age and gender Most patients are between the ages of 25 and 65 years at the time of diagnosis of thyroid carcinoma. Women are affected more often than men (2:1 ratio for the development of both naturally occurring and radiation-induced thyroid cancer).

Etiology and risk factors

Differentiated thyroid cancer

Therapeutic irradiation External low-dose radiation therapy to the head and neck during infancy and childhood, frequently used between the 1940s and 1960s for the treatment of a variety of benign diseases, has been shown to predispose an individual to thyroid cancer. The younger a patient is at the time of radiation exposure, the higher is the subsequent risk of developing thyroid carcinoma. Also, as mentioned previously, women are at increased risk of radiation-induced thyroid cancer. There is a latency period ranging from 10%-30% from the time of low-dose irradiation to the development of thyroid cancer.

As little as 11 cGy and as much as 2,000 cGy of external radiation to the head and neck have been associated with a number of benign and malignant diseases. It was once thought that high-dose irradiation (> 2,000 cGy) to the head and neck did not increase the risk of neoplasia. However, recently it has been shown that patients treated with mantle-field irradiation for Hodgkin lymphoma are at increased risk of developing thyroid carcinoma compared with the general population, although they are more likely to develop hypothyroidism than thyroid cancer.

Radiation-associated thyroid cancer has an identical natural history and prognosis as sporadic thyroid cancer.

Other factors Besides radiation-induced thyroid cancer, there are only sparse data on the etiology of differentiated thyroid cancer.

Signs and symptoms

Most thyroid cancers present as asymptomatic thyroid nodules. Patients may feel pressure symptoms from nodules as they begin to increase in size. A change in the voice can be caused by a thyroid cancer or benign goiter. The voice change usually occurs when there is compression of the larynx or invasion of the recurrent laryngeal nerve.

On physical examination, a thyroid nodule that is hard or firm and fixed may represent a cancer. The presence of palpable enlarged nodes in the lateral neck, even in the absence of a palpable nodule in the thyroid gland, could represent metastases to the lymph nodes.

Diagnostic work-up

As mentioned previously, thyroid nodules are present in 4%-7% of the general population and in a higher percentage of individuals who have had irradiation to the head and neck region. Most thyroid nodules are benign (colloid nodules or adenomas); therefore, it is important for the work-up to lead to surgical resection for malignant nodules and avoid unnecessary surgery for

benign lesions. Although most solid nodules are benign, thyroid carcinomas usually present as solid nodules. A cystic nodule or a "mixed" (cystic-solid) lesion is less likely to represent a carcinoma and more likely to be a degenerated colloid nodule.

In a microarray expression analysis of 28 specimens, papillary and follicular carcinomas appear to have two distinct expression profiles, as compared with normal thyroid tissue. Five genes collectively distinguish the two types of cancers and may eventually aid in the molecular diagnosis of these lesions *(Aldred MA, Huang Y, Liyanarachchi S, et al: J Clin Oncol 22:3531-3539, 2004).*

History The history is very important in the evaluation of thyroid nodules. If there is a history of irradiation to the head and neck, the risk of there being a cancer in the nodule is higher (as great as 50%, compared with a 10%-20% risk in nonirradiated patients).

Age also is important in the evaluation of thyroid nodules. Nodules that occur in either the very young or the very old are more likely to be cancerous, particularly in men.

A new nodule or a nodule that suddenly begins to grow is worrisome as well.

FNA has become the initial diagnostic test for the evaluation of thyroid nodules. First, FNA can determine whether the lesion is cystic or solid. For solid lesions, cytology can yield one of three results: benign, malignant, or indeterminate. The accuracy of cytologic diagnosis from FNA is 70%-80%, depending on the experience of the person performing the aspiration and the pathologist interpreting the cytologic specimen.

In a series of 98 "suspicious" FNAs, findings of cellular atypia (pleomorphism, enlarged nuclei, nuclear grooves, coarse or irregular chromatin, prominent or multiple nucleoli, or atypical or numerous mitotic figures) or follicular lesions with atypia were associated with malignancy 20% and 44% of the time, respectively. Follicular lesions without atypia have a 6.7% risk of malignancy.

Imaging modalities Ultrasonographic and radionuclide (radioiodine and technetium) scans are also used in the evaluation of thyroid nodules.

Ultrasonography can be used to determine whether a nodule is cystic or solid. It cannot differentiate a benign solid nodule from a malignant one but can be used to assess the number of nodules present and their size. A nodule in a gland with multiple other nodules of similar size is unlikely to be malignant. A dominant nodule in a multinodular gland carries a risk of malignancy similar to that of a true solitary nodule. Ultrasonographically guided FNA can be performed, increasing the diagnostic efficacy; it also allows evaluation of cervical lymph nodes.

Thyroid isotope scans cannot differentiate absolutely a benign from a malignant nodule but can, based on the functional status of the nodule, assign a probability of malignancy. "Hot" thyroid nodules (ie, those that concentrate radioiodine) represent functioning nodules, whereas "cold" nodules are nonfunctioning lesions that do not concentrate the isotope. Most thyroid carcinomas occur in cold nodules, but only 10% of cold nodules are carcinomas. It is not necessary to operate on all cold thyroid nodules. CT or MRI scan of

the neck may be appropriate in some cases.

Calcitonin level Medullary thyroid carcinomas usually secrete calcitonin, which is a specific product of the thyroid C cells (parafollicular cells). In patients who have clinically palpable medullary carcinoma, the basal calcitonin level is almost always elevated. In patients with smaller tumors or C-cell hyperplasia, the basal calcitonin level may be normal, but administration of synthetic gastrin (pentagastrin) or calcium results in marked elevation of calcitonin levels. The use of calcitonin levels as a tumor marker and stimulation screening in familial forms of medullary cancers has been largely replaced by genetic testing (see below).

Carcinoembryonic antigen (CEA) Serum CEA levels are elevated in patients with medullary thyroid cancer.

Ruling out pheochromocytoma Medullary thyroid carcinoma can be associated with MEN-2A, MEN-2B, or familial non-MEN. Both the MEN-2A and MEN-2B syndromes are characterized by medullary thyroid cancer and pheochromocytoma. Thus, in any patient with familial medullary thyroid carcinoma, it is imperative that the preoperative work-up include a determination of 24-hour urinary catecholamine levels (metanephrine and vanillylmandelic acid) to rule out the presence of a pheochromocytoma.

Genetic testing Germ-line mutations in the *RET* proto-oncogene are responsible for familial non-MEN medullary thyroid carcinoma in addition to MEN-2A and MEN-2B. DNA analysis performed on a peripheral blood sample is a highly reliable method for identifying the presence of a *RET* mutation. Approximately 95% of patients with *RET* mutation will eventually develop medullary carcinoma of the thyroid, thus prophylactic surgical treatment is recommended. The specific mutated codon of *RET* may correlate with the aggressiveness of medullary carcinoma of the thyroid. This should be considered when counseling affected individuals and their families regarding prophylactic throidectomy and the age at which to perform such surgery. Recommended ages for prophylactic surgery range from within the first 6 months of life to 10 years of age depending on the mutation. The prophylactic surgical procedure of choice is total thyroidectomy with or without central lymph node dissection. Although this approach reflects general recommendations, there remain significant concerns about the ethics and safety of surgery based on genetic testing for this and many other diseases.

Periodic determinations of stimulated calcitonin levels may help make the early diagnosis of medullary thyroid carcinoma in those who do not undergo surgery but will not always prevent the development of metastatic medullary thyroid carcinoma.

Screening

At this time, no organization recommends periodic screening for thyroid cancer using neck palpation or ultrasonography in average-risk, asymptomatic

TABLE 1: UICC staging of thyroid cancer

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 1 cm in greatest dimension, limited to the thyroid
T2	Tumor > 1 cm but not > 4 cm in greatest dimension, limited to the thyroid
T3	Tumor > 4 cm in greatest dimension, limited to the thyroid
T4	Tumor of any size extending beyond the thyroid capsule

Note: All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor (the largest determines the classification).

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis in ipsilateral cervical lymph node(s)
N1b	Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)

Distant metastasis (M)

Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping: Papillary or follicular							**Stage grouping: Medullary**			
	< 45 years old			**≥ 45 years old**						
Stage I	Any T	Any N	M0	T1	N0	M0	Stage I	T1	N0	M0
Stage II	Any T	Any N	M1	T2	N0	M0	Stage II	T2	N0	M0
				T3	N0	M0		T3	N0	M0
Stage III				T4	N0	M0		T4	N0	M0
				Any T	N1	M0	Stage III	Any T	N1	M0
Stage IV				Any T	Any N	M1	Stage IV	Any T	Any N	M1

Stage grouping: Undifferentiated[a]

Stage IV	Any T	Any N	Any M

UICC = International Union Against Cancer

[a] For undifferentiated cancers (eg, anaplastic carcinoma), all cases are classified as stage IV.

adults. However, the ACS recommends examination of the thyroid during a routine checkup, since this surveillance can result in case findings.

Staging and prognosis

Unlike most other cancers, in which staging is based on the anatomic extent of disease, the International Union Against Cancer (UICC) staging of thyroid cancer also takes into consideration patient age at the time of diagnosis and tumor histology (Table 1).

The *ras* gene was analyzed by polymerase chain reaction in 125 thyroid carcinoma specimens. Mutations in the *ras* gene were an independent negative predictor of survival in differentiated thyroid carcinomas (*Garcia-Rostan G, Zhao H, Camp RL, et al: J Clin Oncol 21:3226-3235, 2003*).

Differentiated thyroid cancers Recurrence and death following initial treatment of differentiated thyroid cancer can be predicted using a number of risk classification schemes. The most commonly used systems are the AMES (age, metastases, extent, and size) and AGES (age, grade, extent, and size) classifications.

Low-risk patients are generally those < 45 years of age with low-grade nonmetastatic tumors that are confined to the thyroid gland and are < 1-5 cm. Low-risk patients enjoy a 20-year survival rate of 97%-100% after surgery alone.

High-risk patients are those ≥ 45 years old with a high-grade, metastatic, locally invasive tumor in the neck or with a large tumor. Large size is defined by some authors as > 1 cm and by other authors as > 2 or > 5 cm. The 20-year survival rate in the high-risk group drops to between 54% and 57%.

Intermediate-risk patients include young patients with a high-risk tumor (metastatic, large, locally invasive, or high grade) or older patients with a low-risk tumor. The 20-year survival rate in this group of patients is ~85%.

Medullary thyroid carcinoma is associated with an overall 10-year survival rate of 40%-60%. When medullary carcinoma is discovered prior to becoming palpable, the prognosis is much better: Patients with stage I medullary tumors (ie, tumors < 1 cm or nonpalpable lesions detected by screening and provocative testing) have a 10-year survival rate of 95%.

Stage II medullary cancers (tumors > 1 but < 4 cm) are associated with a survival rate of 50%-90% at 10 years. Patients who have lymph node involvement (stage III disease) have a 10-year survival rate of 15%-50%.

When there are distant metastases (stage IV), the long-term survival rate is compromised. In patients with metastatic medullary thyroid cancer, the disease often progresses at a very slow rate, and patients may remain alive with disease for many years.

Anaplastic thyroid cancer does not have a generally accepted staging system, and all patients are classified as having stage IV disease. Anaplastic carcinoma is highly malignant and has a poor 5-year survival rate (0%-25%). Most patients die of uncontrolled local disease within several months of diagnosis.

Treatment

As most thyroid nodules are not malignant, it is important to differentiate malignant from benign lesions to determine which patients should undergo surgery. If the cytologic result from FNA indicates that the nodule is benign, which is the case most of the time, the nodule can be safely followed. The patient may be placed on thyroxine therapy to suppress thyroid-stimulating hormone (TSH) and reevaluated in 6 months. Adequate suppression is considered to be a TSH level of 0.2-0.4 μU/mL for 6 months.

SURGERY

Malignant or indeterminate cytologic features are the main indications for surgery.

Malignant nodule

Differentiated thyroid cancer If the cytologic result shows a malignant lesion, thyroidectomy should be performed. There is significant debate in the literature regarding the extent of thyroid surgery for primary tumors confined to one lobe. The surgical options include total lobectomy, total lobectomy with contralateral subtotal lobectomy (subtotal thyroidectomy), or total thyroidectomy. The decision about which procedure to perform should be based on the risk of local recurrence and the anticipated use of radioactive iodine (see section on "Radioactive I-131").

Most authorities agree that a good-risk patient (age < 45 years) with a 1-cm or smaller papillary thyroid cancer should undergo ipsilateral total lobectomy alone. Most experts also agree that total thyroidectomy (or at least subtotal thyroidectomy) is appropriate for high-risk patients with high-risk tumors. Intermediate-risk patients are treated with total lobectomy alone or total (or subtotal) thyroidectomy plus postoperative radioactive iodine. Preoperative neck imaging may help plan the surgery.

The necks of all patients should be palpated intraoperatively. If positive nodes are found, a regional lymph node dissection should be performed.

Medullary carcinoma Patients with medullary thyroid cancer should be treated with total thyroidectomy and a sampling of the regional nodes. If there is involvement of the nodes, a modified neck dissection should be performed (see section on "Lymph node dissection"). If the cancer is confined to the thyroid gland, the patient is usually cured. Postoperative adjuvant external irradiation may be used in certain circumstances (see section on "External radiation therapy").

Anaplastic carcinoma A tracheostomy often is required in patients with anaplastic thyroid cancer because of compression of the trachea. If the tumor is confined to the local area, total thyroidectomy may be indicated to reduce local symptoms produced by the tumor mass. Radiation therapy is used to improve locoregional control, often together with radiosensitizing chemotherapy.

Indeterminate or suspicious nodule

The nodule that yields indeterminate or suspicious cytologic results and is cold on thyroid scanning should be removed for histologic evaluation. The initial operation performed in most patients should be total lobectomy, which entails removal of the suspicious nodule, hemithyroid, and isthmus. The specimen can be sent for frozen-section analysis during surgery. If the diagnosis is a colloid nodule, no further resection of the thyroid is required.

Follicular lesion If frozen-section biopsy results indicate a follicular lesion in a patient who is a candidate for total thyroidectomy, and a decision cannot be made as to whether the lesion is benign or malignant, two options are available: (1) stop and wait for final confirmation of the diagnosis, which may require a future operation; or (2) proceed with subtotal or total thyroidectomy, which obviates the need for a later operation.

Hürthle cell carcinoma If the nodule is diagnosed as a Hürthle cell carcinoma, total thyroidectomy is generally recommended for all large (> 4 cm) invasive lesions. Small lesions can be managed with total lobectomy. However, controversy remains over the optimal treatment approach for this cancer.

Lymph node dissection

Therapeutic dissection Therapeutic central neck node dissection should be performed for medullary carcinomas and other thyroid neoplasms with nodal involvement. The dissection should include all the lymphatic tissue in the pretracheal area and along the recurrent laryngeal nerve and anterior mediastinum. If there are clinically palpable nodes in the lateral neck, a modified neck dissection is performed.

Prophylactic dissection There is no evidence that performing prophylactic neck dissection improves survival. Therefore, aside from medullary thyroid cancer patients, who have a high incidence of involved nodes, only therapeutic neck dissection is indicated.

Removal of individual abnormal nodes ("berry picking") is not advised when lateral neck nodes are palpable because of the likelihood of missing involved nodes and disrupting involved lymphatic channels.

Metastatic or recurrent disease

Survival rates from the time of the discovery of metastases (lung and bone) from differentiated thyroid cancer are less favorable than those associated with local recurrence (5-year survival rates of 38% and 50%, respectively). Survival also depends on whether the metastatic lesions take up I-131.

Surgery, with or without I-131 ablation (discussed below), can be useful for controlling localized sites of recurrence. Approximately half of patients who undergo surgery for recurrent disease can be rendered free of disease with a second operation.

RADIOACTIVE I-131

Uses in papillary or follicular thyroid carcinoma

There are two basic uses for I-131 in patients diagnosed with papillary or follicular thyroid carcinoma: ablation of normal residual thyroid tissue after thyroid surgery and treatment of thyroid cancer, either residual disease in the neck or metastasis to other sites in the body. It should be emphasized that patients with medullary, anaplastic, and most Hürthle cell cancers do not benefit from I-131 therapy.

Postoperative ablation of residual thyroid tissue should be considered in high-risk patients and patients with high-risk tumors. Ablation of residual normal thyroid tissue allows for the use of I-131 scans to monitor for future recurrence, possibly destroys microscopic foci of metastatic cancer within the remnant, and improves the accuracy of thyroglobulin monitoring.

Bal et al have conducted a randomized trial of ablative doses of radioactive iodine and concluded that any dose between 25 and 50 mCi is adequate for remnant ablation *(Bal CS, Kumar A, Pant GS: J Clin Endocrinol Metab 89:1666-1673, 2004).*

Ablation must also be accomplished in patients with regional or metastatic disease prior to the use of I-131 for treatment, as the normal thyroid tissue will preferentially take up iodine compared to the cancer.

Following surgery, the patient should not be given thyroid hormone replacement. The TSH level should be determined approximately 4-6 weeks after surgery; in patients who underwent total or subtotal thyroidectomy, TSH levels will generally be > 50 μU/mL. A postoperative iodine scan can then be performed. If this scan documents residual thyroid tissue, an ablative dose of I-131 should be given. The patient should be advised not to undergo any radiographic studies with iodine during ablation therapy and to avoid seafood and vitamins or cough syrups containing iodine. Patients are prepared with a specific diet prior to the I-131 therapy. Iodine-123 may also be used in the postoperative setting. It may produce a better image quality than I-131 scans.

Iodine-131 dose In general, doses up to 75-100 mCi will ablate residual thyroid tissue within 6 months following ingestion. In some patients, it may take up to 1 year for complete ablation to occur. Patients should be monitored following ablation, and when they become hypothyroid, hormone replacement therapy should be given until they are clinically euthyroid and TSH is suppressed. Recently, lower doses have been found to be effective. TSH levels should be < 0.1 μU/mL.

Barbaro et al have reported on the use of recombinant human thyrotropin stimulation with 30 mCi of I-131 for remnant ablation *(Barbaro D, Boni G, Meucci G, et al: J Clin Endocrinol Metab 89:4110-4115, 2003).*

Follow-up I-131 scan Approximately 6-12 months after ablation of the thyroid remnant, a follow-up I-131 scan should be performed. Recombinant human thyrotropin alpha (Thyrogen) is now available. Patients may continue on thyroid replacement and receive two doses of thyrotropin prior to I-131 scanning; this approach can prevent the symptoms of hypothyroidism.

Pacini et al have recommended the use of human thyrotropin-stimulated serum thyroglobulin and neck ultrasonography as follow-up for differentiated thyroid carcinoma *(Pacini F, Molinaro E, Castagna MG, et al: J Clin Endocrinol Metab 88:3668-3673, 2003).*

Treatment of residual cancer For disease in the tumor bed or lymph nodes, an I-131 dose of 100-150 mCi is given. For disease in the lungs or bone, the I-131 dose is 200 mCi. Following this therapy, the patient is again put on thyroid hormone replacement, and adequate suppression is maintained by monitoring TSH levels.

PET scan may be useful in identifying metastatic disease. Twenty patients treated with total thyroidectomy and I-131 who presented with elevated serum thyroglobulin levels but a normal I-131 scan were studied with PET. PET identified hypermetabolic metastases in 17 patients (85%), whereas 2 patients with miliary lung metastases had a normal scan *(Hung MC, Wu HS, Kao CH, et al: Endocr Res 29:169-175, 2003).*

Follow-up Some clinicians advocate obtaining a repeat scan in 1 year, along with a chest x-ray, and repeating this procedure until a normal scan is obtained. However, the frequency of repeat scans and the dose of I-131 are rather controversial and should be guided by the individual's risk profile.

Following thyroid remnant ablation, serum thyroglobulin measurements are useful in monitoring for recurrence. Since thyroglobulin in a patient receiving thyroid hormone replacement may be suppressed, a normal test may be incorrect ~10% of the time. In general, the presence of disease is accurately predicted by a thyroglobulin value > 5 ng/mL while the patient is in the suppressed state and by a value > 10 ng/mL in the hypothyroid state. However, measurable disease may not be identified in many patients. Whether or not they should be treated on the basis of the thyroglobulin value if the I-131 scan is normal is a subject of current debate.

Chest x-rays should continue to be performed at yearly intervals for at least 10 years. Neck ultrasonography is also useful to evaluate locoregional recurrence. Continued monitoring is necessary, as late recurrence can occur. It should be pointed out that certain aggressive tumors may neither be radioactive iodine–avid nor synthesize thyroglobulin. PET scanning may contribute to localization of disease in some cases and may even carry prognostic value.

Side effects and complications

Acute effects The acute side effects of I-131 therapy include painful swelling of the salivary glands and nausea. Ibuprofen or other pain relievers are usually used to decrease salivary gland discomfort. Nausea may be treated with standard antiemetics.

Rarely, in patients with significant residual thyroid tissue, radioactive iodine may cause acute thyroiditis due to a rapid release of thyroid hormone. This problem can be treated with steroids and β-blockers.

Patients must also be cautioned not to wear contact lenses for at least 3 weeks following ingestion of I-131, as the tears are radioactive and will contaminate the lenses and possibly lead to corneal ulceration.

Bone marrow suppression and leukemia are potential long-term complications of I-131 therapy but are poorly documented and appear to be extremely rare. Patients should have a CBC count performed prior to ingestion of an I-131 dose to ensure adequate bone marrow reserve. They should also have yearly blood counts. Leukemia occurs rarely with doses of I-131 < 1,000 mCi.

Pulmonary fibrosis may be seen in patients with pulmonary metastases from papillary or follicular thyroid cancer who are treated with I-131. Those with a

miliary or micronodular pattern are at greater risk, as a portion of normal lung around each lesion may receive radiation, leading to diffuse fibrosis.

Effects on fertility Recent data have documented an increase in follicle-stimulating hormone (FSH) levels in one-third of male patients treated with I-131. Changes in FSH after one or two doses of I-131 are generally transitory, but repeated doses may lead to lasting damage to the germinal epithelium.

The effects of I-131 on female fertility have been investigated. A recently published article showed no significant difference in the fertility rate in women receiving radioactive iodine. However, it is generally recommended to avoid pregnancy for 1 year after therapeutic I-131 administration.

No ill effects have been noted in the offspring of treated patients.

EXTERNAL RADIATION THERAPY

Papillary or follicular thyroid cancer

There are a number of indications for external irradiation of papillary or follicular thyroid carcinoma. Surgery followed by radioactive iodine may be used for disease that extends beyond the capsule. However, if all gross disease cannot be resected, or if residual disease is not radioactive iodine–avid, external irradiation is used as part of the initial approach for locally advanced disease in older patients.

Unresectable disease External irradiation is useful for unresectable disease extending into the connective tissue, trachea, esophagus, great vessels, and anterior mediastinum. For unresected disease, doses of 6,000-6,500 cGy are recommended. The patient should then undergo I-131 scanning, and, if uptake is detected, a dose of I-131 should be administered.

Recurrence after resection External irradiation may also be used after resection of recurrent papillary or follicular thyroid carcinoma that no longer shows uptake of I-131. In this situation, doses of 5,000-6,000 cGy are delivered to the tumor bed to prevent local recurrence. Multiple-field techniques and extensive treatment planning are necessary to deliver high doses to the target volume without the risk of significant complications.

Palliation of bone metastases External radiation therapy is useful in relieving pain from bone metastasis. If the metastasis shows evidence of I-131 uptake, the patient should be given a therapeutic dose of I-131 followed by local external radiation therapy to the lesion of up to 4,000-5,000 cGy. Ten thyroid cancer patients with bone metastasis were treated with monthly pamidronate (Aredia). The patients experienced a significant decrease in bone pain and improved quality of life.

Anaplastic thyroid carcinoma

Anaplastic carcinoma of the thyroid is an exceptionally aggressive disease. It often presents as a rapidly expanding mass in the neck and may not be completely resected. External irradiation to full dose (6,000-6,500 cGy) may slow the progress of this disease but rarely controls it.

Chemoradiation therapy There are reports of the use of accelerated fractionation regimens of external irradiation (160 cGy twice daily to 5,700 cGy) with weekly doxorubicin in patients with anaplastic thyroid cancer, as well as reports of the combination of doxorubicin and cisplatin with external irradiation. These regimens have improved local control but at the expense of increased toxicity. Unfortunately, the majority of patients die of progressive disease.

Medullary thyroid carcinoma

External irradiation has been used for medullary thyroid cancer in the postoperative setting. Indications include positive surgical margins, gross residual disease, or extensive lymph node metastasis. The recommended dose is 5,000 cGy in 5 weeks.

ROLE OF MEDICAL THERAPY

Differentiated thyroid cancer

Thyroid hormone replacement As mentioned previously, thyroid hormone replacement is used to suppress TSH in most patients with differentiated thyroid cancer after surgery and prior to I-131 scanning and (as appropriate) treatment.

Systemic chemotherapy is used for widespread disease, although reproducibly effective regimens have not been identified to date.

Medullary thyroid carcinoma

In patients with medullary thyroid carcinoma, the usual treatment is surgery. In patients with familial medullary carcinoma who have a coexisting pheochromocytoma, appropriate control of catecholamine hypersecretion should precede thyroid surgery.

Anaplastic thyroid carcinoma

As mentioned previously, the usual treatment for patients with resectable or localized anaplastic thyroid cancer is surgery. Like radiotherapy, chemotherapy is an important alternative approach, but further evaluation is needed to optimize its effectiveness.

PARATHYROID CARCINOMA

Parathyroid carcinoma is a rare cause of hypercalcemia, accounting for < 2% of cases with primary hyperparathyroidism.

Epidemiology and etiology

The disease presents in midlife and occurs with similar frequency in both genders. The etiology of parathyroid carcinoma is obscure; an association with prior neck irradiation is not apparent. Treatment of parathyroid carcinoma is primarily surgical.

Signs and symptoms

Most patients with parathyroid cancer have symptomatic moderate to severe hypercalcemia (mean serum calcium level, 15 mg/dL) and high parathyroid hormone levels. They often present with a palpable neck mass. Unlike benign hyperparathyroidism, renal and bone abnormalities are more common in patients with parathyroid cancer.

Rarely, nonfunctioning tumors may present as neck masses; their clinical course is similar to that of functioning tumors. Clinical concern about parathyroid cancer should be raised in the presence of a palpable neck mass and severe hypercalcemia, recurrent hyperparathyroidism, or associated vocal cord paralysis.

Pathology

The principal features of parathyroid cancer include a trabecular pattern, mitotic figures, thick fibrous bands, and capsular or vascular invasion of disease. Other important features include lymphatic or hematogenous metastases and histologic evidence of tumor infiltration into the surrounding tissues (including macroscopic adherence or vocal cord paralysis).

Although cytologic evidence of mitoses is necessary to establish the diagnosis of carcinoma, mitotic activity alone is an unreliable indicator of malignancy. The only reliable microscopic finding of malignancy is invasion of surrounding structures or metastasis to lymph nodes or other organs.

Treatment

Surgical treatment of primary hyperparathyroidism

The diagnosis of parathyroid carcinoma is sometimes made during surgical exploration for primary hyperparathyroidism. Most surgeons advocate identification of all four parathyroid glands. In most cases, the upper glands can be found on the posterior aspect of the upper third of the thyroid lobe, just cephalad to the inferior thyroid artery and adjacent to the recurrent laryngeal nerve as it enters the larynx.

The inferior parathyroid glands are more variable in location. Most are found on the posterior or lateral aspect of the lower pole of the thyroid gland, but the inferior parathyroid glands may be ectopically placed in the superior or true mediastinum, often within the thymus.

The inferior and, less commonly, superior glands can be located in an ectopic location in the upper or lateral neck, adjacent to the esophagus, or within the carotid sheath.

Surgical exploration for primary hyperparathyroidism Most cases of primary hyperparathyroidism are caused by a single hyperfunctioning parathyroid adenoma. If the surgeon finds one (or occasionally two) enlarged abnormal gland(s) and the remaining glands are normal, the enlarged gland should be removed.

If four enlarged glands are found, indicating the rare case of primary parathyroid hyperplasia, subtotal parathyroidectomy including 3.5 glands should be performed. Consideration should be given to transplanting the remaining gland remnant to an ectopic location that would be easily accessible to the surgeon if hyperparathyroidism recurs.

If only normal glands are found at exploration, a missed adenoma in an ectopic location should be suspected. Thorough intraoperative neck and superior mediastinal exploration should be performed, and if the missing gland cannot be found, thymectomy and hemithyroidectomy should be performed to exclude an intrathymic or intrathyroidal adenoma. Localization studies, including CT/MRI or radionuclide imaging, should precede reexploration for a missed adenoma.

Intraoperative parathyroid (iPTH) levels are increasingly used to guide surgery for primary hyperparathyroidism. A 50% or greater decrease in iPTH level from the preexcision value to the 10-minute postexcision value is used as a predictor of successful surgery. Based on this information, many surgeons advocate an image-guided, unilateral neck exploration with iPTH analysis.

The use of iPTH with parathyroid hyperplasia requires more strict evaluation of iPTH levels. Siperstein et al performed a prospective evaluation of iPTH and bilateral neck exploration and found that up to 15% of cases will have additional "abnormal" glands that were not predicted by iPTH or preoperative imaging. This study demonstrates the need for long-term follow-up of patients undergoing focused parathyroid surgery.

If parathyroid carcinoma is suspected, based on the severity of hyperparathyroidism or invasion of surrounding tissues by a firm parathyroid tumor, aggressive wide excision is indicated. This procedure should include ipsilateral thyroidectomy and en bloc excision of surrounding tissues as necessary.

Patterns of recurrence of cancer The average time from initial surgery to the first recurrence of cancer is approximately 3 years but may be as long as 10 years. The thyroid gland is the usual site of involvement, with disease "seeding" in the neck a common pattern. Other sites of involvement include the recurrent nerve, strap muscles, esophagus, and trachea.

Distant metastases can be present at the time of initial surgery, or local spread to contiguous structures in the neck may be followed subsequently by distant metastases to the lungs, bone, and liver.

In a recent analysis, 85% of patients with parathyroid carcinoma were alive 5 years after diagnosis; death usually results from complications of the hypercalcemia rather than from the tumor burden.

Treatment of isolated metastases Isolated metastases should be aggressively resected to enhance survival and control hypercalcemia.

Medical therapy

Morbidity and mortality are generally caused by the effects of unremitting hypercalcemia rather than tumor growth. Medical treatment provides temporary palliation of hypercalcemia. Drugs used include bisphosphonates, such as pamidronate (60-80 mg q4-6d) or zoledronic acid (Zometa); calcitonin, 4-8 IU/kg q6-12h; mithramycin (plicamycin [Mithracin]), 25 µg/kg q4-6d; and gallium nitrate (Ganite), 100-200 mg/m^2/d IV for 5 days.

SUGGESTED READING

ON THYROID CARCINOMA

Alsanea O, Clark OH: Familial thyroid cancer. National Library of Medicine. Curr Opin Oncol 13:44–51, 2001.

Bal CS, Kumar A, Pant GS: Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: A randomized clinical trial in 509 patients. J Clin Endocrinol Metab 89:1666–1673, 2004.

Berg G, Lindstedt G, Suurkula M, et al: Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid-stimulating hormone. J Endocrinol Invest 25:44–52, 2002.

Chow SM, Law SC, Mendenhall WM, et al: Prognostic factors and the role of radioiodine and external radiotherapy. Int J Radiat Oncol Biol Phys 52:784–795, 2002.

Pacini F, Molinaro E, Lippi F, et al: Prediction of disease status by recombinant human TSH-stimulated serum Tg in the postsurgical follow-up of differentiated thyroid carcinoma. J Clin Endocrinol Metab 86:5686–5690, 2001.

Goldstein RE, Netterville JL, Burkey B, et al: Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of thyroid nodules. Ann Surg 235:656–662, 2002.

Guiffrida D, Gharib H: Anaplastic thyroid carcinoma: Current diagnosis and treatment. National Library of Medicine. Ann Oncol 11:1083–1089, 2000.

Haigh PI, Ituarte PH, Wu HS, et al: Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer 91:2335–2342, 2001.

Haugen BR, Lin EC: Isotope imaging for metastatic thyroid cancer. Endocrinol Metab Clin North Am 30:469–492, 2001.

Kuriakose MA, Hicks Jr WL, Loree TR, et al: Risk group-based management of differentiated thyroid carcinoma. J R Coll Surg Edinb 46:216–223, 2001.

Larson SM, Robbins R: Positron emission tomography in thyroid cancer management. Semin Roentgenol 37:169–174, 2002.

Luster M, Lassmann M, Haenscheid H, et al: Use of recombinant human thyrotropin before radioiodine therapy in patients with advanced differentiated thyroid carcinoma. J Clin Endocrinol Metab 85:3640–3645, 2000.

Mazzaferri EL, Kloos RT: Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. National Library of Medicine. J Clin Endocrinol Metab 86:1447–1463, 2001.

Mazzaferri EL, Robbins RJ, Spencer CA, et al: A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 88:1433–1441, 2003.

Pacini F, Capezzone M, Elisei R, et al: Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 87:1499–1501, 2002.

Pacini F, Elisei R, Romei C, et al: *RET* proto-oncogene mutations in thyroid carcinomas: Clinical relevance. National Library of Medicine. J Endocrinol Invest 23:328–338, 2000.

Sautter-Bihl ML, Raub J, Hetzel-Sesterheim M, et al: Differentiated thyroid cancer: Prognostic factors and influence of treatment on the outcome in 441 patients. Strahlenther Onkol 177:125–131, 2001.

Tennvall J, Lundell G, Wahlberg P, et al: Anaplastic thyroid carcinoma: Three protocols combining doxorubicin, hyperfractionated radiotherapy, and surgery. Br J Cancer 86:1848–1853, 2002.

Torlontano M, Attard M, Crocetti U, et al: Follow-up of low risk patients with papillary thyroid cancer: Role of neck ultrasonography in detecting lymph node metastases. J Clin Endocrinol Metab 89:3402–3407, 2004.

Vitale G, Caraglia M, Ciccarelli A, et al: Current approaches and perspectives in the therapy of medullary thyroid carcinoma. Cancer 91:1797–1808, 2001.

Wang W, Larson SM, Fazzari M, et al: Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab 85:1107–1113, 2000.

Wu HS, Young MT, Ituarte PH, et al: Death from thyroid cancer of follicular cell origin. J Am Coll Surg 191:600–606, 2000.

ON PARATHYROID CARCINOMA

Busaidy N, Jimenez C, Habra MA, et al: Parathyroid carcinoma: A 22-year experience. Head Neck 26:716–726, 2004.

Dackiw AP, Sussman JJ, Fritsche HA Jr, et al: Relative contributions of technetium Tc 99m sestamibi scintigraphy, intraoperative gamma probe detection, and the rapid parathyroid hormone assay to the surgical management of hyperparathyroidism. Arch Surg 135:550–557, 2000.

Dotzenrath C, Goretzki PE, Sarbia M, et al: Parathyroid carcinoma: Problems in diagnosis and the need for radical surgery even in recurrent disease. Eur J Surg Oncol 27:383–389, 2001.

Hundahl SA, Fleming ID, Fremgen AM, et al: Two hundred eighty-six cases of parathyroid carcinoma treated in the US between 1985-1995: A National Cancer Data Base Report. Cancer 86:538–544, 1999.

Rolighed L, Heickendorff L, Hessov I, et al: Primary hyperparathyroidism: Intraoperative PTH-measurements. Scand J Surg 93:43–47, 2004.

Shane E: Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab 86:485–493, 2001.

Sheehan JJ, Hill AD, Walsh MF, et al: Parathyroid carcinoma: Diagnosis and management. Eur J Surg Oncol 27:321–324, 2001.

Siperstein A, Berber E, Mackey R, et al: Prospective evaluation of sestamibi scan, ultrasonography, and rapid PTH to predict the success of limited exploration of sporadic primary hyperparathyroidism. Surgery 136:872–880, 2004.